Systems biology – current status and challenges

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We have put together a special issue on current approaches in systems biology with a focus on mathematically modeling of metabolic networks. Mathematical models have been increasingly used to unravel molecular mechanisms of complex dynamic biological processes. We here provide a short introduction into the topics covered in this special issue, highlighting current developments and challenges.

Systems biology has a wide range of definitions and covers an even wider range of different approaches and topics. We here refer to systems biology as an area of research that uses mathematical modelling in tight interconnection with experimental approaches to understand the mechanisms of complex biological systems and predict their behavior across scales – molecular-to-organismal. This special issue focusses on metabolic modelling within this context where topics range from single cell systems to multi-tissue and whole-body models. There are generally two different approaches to metabolic modelling. One is the dynamical modelling of detailed targeted pathways using kinetic rate laws, which allows us to describe steady state fluxes and the dynamics of metabolite concentrations. As kinetic rates are often measured only for a limited number of reactions, these models usually cover only a small part of cellular metabolism. These approaches are also often used to describe signal transduction pathways. Interestingly, most dynamic models to date have been built for higher eukaryotes, mainly mammals. In contrast, whole cell or genome-wide metabolic models are still mainly used to analyze microbial systems. Genome scale modelling approaches describe the whole cell metabolic networks using methods known as 'constraint based metabolic modelling'. The latter are largely based on the assumption of evolutionary optimality of cellular metabolism. The disadvantage of these models is that the concentration of modelled internal metabolites – those that do not represent sources or sinks to the system – cannot be considered independently from each other. In addition, simulations of this type strongly depend on the particular assumptions made about optimization and corresponding optimization functions used to constrain the solution space. To overcome these limitations, more research groups have engaged 'hybrid modeling approaches', either scaling up of dynamic models or simplifying genome scale models. Targeting the latter, the review provided by Singh and Lercher [1] discusses model reduction strategies that shall enable detailed dynamic description of genome scale metabolism through model reduction.

Notwithstanding drawbacks, both dynamic and genome-scale metabolic modeling approaches have been very successful in both biotechnology and for the prediction of metabolic alteration in disease. A number of different approaches and model systems, ranging from bacteria to human are presented in this special issue:

De Groot et al. [2] analyze general metabolic features of model organisms, such as *Escherichia coli* and *Saccharomyces cerevisiae*. By comparing several models available to date, they identify modeling constraints that lead to the robust prediction of the often-discussed counterintuitive effect of overflow metabolism. In contrast, Park et al. [3] discuss why pathogenetic bacteria such as Pseudomonads in isolation or bacterial communities often behave differently than the model organisms and show that their (evolutionary) success may be achieved through the adaptation of alternative metabolic strategies with respect to nutrient usage. The reviews by Ewald et al. [4] and Pecht et al. [5], build upon multicellular and multi-species systems by reviewing current modelling approaches to study host-pathogen interactions. In recent years, there has been a concerted effort to improve our understanding of the metabolism of multicellular eukaryotes, such as humans or plants. Although examples of genome-scale modelling exist for these systems, their predictive capacity still remains behind those for single cell organisms. Thus, dynamic metabolic modelling approaches describing specific pathways of interest are very common. As an example, Mazat et al. [6] provide a review of modelling approaches and current knowledge of ROS production in mitochondria. While there are fewer plant studies compared to human and mammalian ones, an increasing number of systems biology studies are looking into resistance of plants to environmental stress and accompanying metabolic/nutritional changes. In this respect, Holzheu and Kummer [7] review current modelling approaches used to study the model plant *Arabidopsis thaliana* and provide examples on how they have increased our understanding of plant metabolism and their potential for agricultural and medical practice.

Most models to date, only target one level of organization, and real multiscale approaches are still limited. One reason is, that the level of detail needs to be adjusted when going from single cell, over multi-cellular systems and tissues to the whole-body level, which requires to make assumptions that in turn may limit the predictive capacity and the possibilities for emerging behavior. As part of this special issue, Shaw and Cheung [8] discuss the advantages and disadvantages of multi-tissue whole plant modelling approaches in comparison to single tissue approaches.
Challenges for multiscale modelling approaches do not only arise from limitations in our ability to mathematically represent a biological system. The challenges are inherent to the complex biology observed in many of our study systems and from limitations imposed from experimental observation. Different techniques need to be used to study different levels of organization. Sometimes experimental data is only available from *in vitro* studies, while *in vivo* measurement can be very different or impossible. This topic is discussed in the review provided by Clarelli et al. [9], which emphasizes these limitations in the context of predicting *in vivo* antibiotic responses.

The reviews provided in this special issue cover many different methods and examples, in which systems biology was used to further our understanding of biology. Many more have been developed in recent years, covering all levels of organization, time scales as well as using different mathematical approaches, ranging from cellular automata to logical networks. As the field has expanded and more researchers have started using systems biology approaches in their work, the number of meetings covering systems biology has also increased. For example, the conferences of the International Study Group for Systems Biology (ISGSB – isgsb.org), which also served as the seed for this special issue, are held on a biannual basis, whereas the larger International Conference in Systems Biology (ICSB) is held every year. The next ISGSB conference will be held in Stellenbosch, South Africa from the 14th to 19th of September 2020, whereas the next ICSB will be held in Connecticut from 10th to 16th of October 2020 (http://icsb2020.bioscience-ct.net/).

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